REMARKS

Claims 4, 5, 8, 15, and 30-40 are pending, and were rejected by the Examiner. Claims 4 and 32 have been amended to recite methods of determining the likelihood of progression of a multiple myeloma-related plasmaproliferative disorder (MMRPD) in an individual to multiple myeloma (MM). Claim 15 has been amended to recite a method for determining the status of MM in an individual. Support for these amendments can be found in Applicants' specification at, for example, page 3, lines 26-27, page 9, lines 7-10, page 19, lines 1-2, and page 19, line 27 to page 20, line 2. In addition, the methods of claims 4, 8, 15, 32, and 36-40 have been amended to include using a bone marrow preparation supernatant. Furthermore, claims 5, 30, 31, and 33-35 have been amended to recite that the MMRPD is in the individual referred to in the respective base claims.

In addition, new claims 41-44 recite methods for determining the likelihood of progression of a multiple myeloma-related plasmaproliferative disorder in an individual to multiple myeloma, wherein the methods include measuring IL-6 production by stromal cells cultured with earlier and later bone marrow preparation supernatants from the individual. Support for claims 41-44 can be found in Applicants' specification at, for example, page 10, lines 1-12, and page 11, lines 25-28. No new matter has been added by these amendments.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 4, 5, 8, 15, and 30-44.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 4, 5, 8, 15, and 30-40 under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner stated that the claims fail to recite a step of combining the bone marrow preparation with the stromal cells. The Examiner also alleged that it is not clear what is meant by "bone marrow preparation," and that the claims fail to accurately recite the details of the assay. Furthermore, the Examiner stated that claims 5, 30, 31, and 33-35 lack proper antecedent basis for the reference to the condition, and suggested that

the phrase "in said individual" be added after "multiple myeloma related plasmaproliferative disorder" in these claims.

With respect to the amended claims, Applicants respectfully disagree with the Examiner's comments regarding the step of combining the bone marrow preparation with the stromal cells. Applicants have amended claims 4, 8, 15, 32, and 36-40 to recite using a "bone marrow preparation supernatant" in the claimed methods. Thus, the claimed methods include quantitating IL-6 production by stromal cells cultured with bone marrow preparation supernatants. It is entirely clear that the stromal cells are combined with the bone marrow preparation supernatants in the presently claimed methods. In addition, claims 8 and 36-40 further specify that the bone marrow preparation supernatants are from cultured bone marrow cells. Thus, the meaning of "bone marrow preparation" is clear.

In response to the Examiner's statement regarding antecedent basis for the reference to the condition in claims 5, 30, 31, and 33-35, Applicants have amended these claims to include the phrase "in said individual" after the reference to MMRPD, as suggested by the Examiner.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 4, 5, 8, 15, and 30-40 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 4, 5, 8, 15, and 30-40 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. In particular, the Examiner stated that it is not clear that the term "monitoring the status" is supported by Applicants' specification. The Examiner suggested that the language could be changed to relate to determining whether a MMPRD in an individual is likely to progress to active MM.

In accordance with the Examiner's suggestion, Applicants have amended claims 4 and 32 to recite methods for determining the likelihood of progression of a MMRPD to MM in an individual. Applicants also have amended claim 15 to recite a method for determining the status of MM in an individual. In light of these amendments, Applicants respectfully request withdrawal of the rejection of claim 4, 5, 8, 15, and 30-40 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 4, 5, 8, 15, and 30-40 under 35 U.S.C. § 103(a) as being unpatentable over Donovan (1998 *Leukemia* 12:593-600) and Carter (1990 *Br. J. Haematol.* 74:424-431). The Examiner asserted that the Donovan reference teaches that IL-1β can be used to differentiate between diagnoses of MM, MGUS, and an unrelated condition, and that IL-1β and IL-6 have a functional relationship in MM. The Examiner further asserted that while the Donovan reference does not teach a stromal cell assay, the Carter reference teaches a stromal cell co-culture using purified myeloma cells and marrow stromal cells. In addition, the Examiner asserted that the Carter reference teaches that IL-6 is produced in direct proportion to IL-1β in the co-culture, and that the production of IL-6 is blocked by antibodies against IL-1β. Thus, the Examiner alleged that it would have been *prima facie* obvious to use the criteria of the Donovan reference and the assay of the Carter reference to determine the status of an individual with MMRPD.

Applicants respectfully disagree. The criteria that must be met in order to establish a case of *prima facie* obviousness include the following: (1) there must be some motivation to modify or combine reference teachings, and (2) there must be a reasonable expectation of success. See, MPEP §§ 2143.01 and 2143.02. The references cited by the Examiner fail to satisfy either of these requirements.

The fact that references can be combined does not render the resulting combination obvious unless the prior art suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990), and MPEP § 2143.01. The presently claimed methods include measuring IL-6 production by normal stromal cells cultured with a patient bone marrow preparation supernatant. Support for such indirect co-culture methods can be found in Applicants' specification at, for example, page 11, lines 3-16, and page 17, lines 20-30. In contrast, the Donovan reference discloses a direct assay of IL-6 and IL-1β expression in patient bone marrow preparations. Stromal cells that produce IL-6 in such preparations presumably have been exposed to cytokines produced by other bone marrow cells before removal from the

patient. The Donovan reference provides no suggestion to apply a patient bone marrow preparation to normal stromal cells that have not previously been exposed to cytokines produced within a patient. Furthermore, the Donovan reference does not suggest using such an assay to evaluate the likelihood of progression from MMRPD to MM in an individual. The Carter reference fails to correct the deficiencies of the Donovan reference. Thus, the cited references fail to provide any suggestion for combining the method of Donovan with the assay of Carter.

The references cited by the Examiner also fail to provide a reasonable expectation of success for determining the likelihood of progression of MMRPD to MM in an individual. As shown in Tables 2 and 4 of the Donovan reference, for example, IL-6 and IL-1β were detectable in only a low percentage of bone marrow preparations from patients without MM. In addition, the Donovan reference states, "Follow-up of IL-1β-positive MGUS patients such as this individual may determine whether aberrant expression of IL-1β is predictive of progression to active MM." See, the second paragraph on page 599. The Donovan reference also states, "In the future, continued follow-up of IL-1β-positive and -negative MGUS patients should determine whether aberrant expression of IL-1β by monoclonal plasma cells is a critical genetic event in the progression of MGUS to myeloma." See, the final paragraph on page 599. These statements demonstrate the uncertainty about whether or how to monitor the status and predict the progression of MMRPD patients. Thus, the Donovan reference in light of the Carter reference does not provide a reasonable expectation of success for the methods recited in the present claims, particularly in view of the data presented in Tables 2 and 4 of Donovan. It is only with hindsight based upon a reading of Applicants' specification that the present invention can be considered obvious in view of the cited references.

Thus, the amended claims are not obvious over the Donovan reference in light of the Carter reference. In light of the above, Applicants respectfully request withdrawal of the rejection of claims 4, 5, 8, 15, and 30-40 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully submit that claims 4, 5, 8, 15, and 30-44 are in condition for allowance, which action is requested. The Examiner is invited to telephone the undersigned at the number provided below if such would further prosecution.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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